<center>**Molecular Simulation Lecture Notes**

By

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Read these lecture notes after going through the introductory statistical thermodynamics notes.

Disclaimer: The notes do not contain everything that was taught in the class.

References:

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Statistical thermodynamics based molecular simulation techniques

Monte Carlo Simulations

Simple or Random sampling Monte Carlo technique

The basic objective is to calculate $E \leftrightarrow \bar{E} = \sum_{i=1}^{N} p_i E_i$ for a large system. At this stage we assume that E_i for the 'i'th microstate is already known to us through some technique. Then the central problem is to find the p_i's for the most probable distribution of microstates of the system. Random sampling involves taking the average of the energies of random microstates of the system. Note the number of microstates is extremely large and computationally it is nearly impossible to take the average of all possible states. I now give the algorithm of this technique.

The algorithm

1. We construct the initial configuration of the simulation cell by randomly placing molecules at any position in the cell. Since the molecules are placed randomly, therefore, overlap can always happen. The simulation cell is of fixed volume and

<center>1</center>

contains a constant number of molecules to construct a system of given density. Calculate the energy of this microstate (or configuration) of the system using the Lennard-Jones potential.

2. Randomly choose a molecule out of those in the system and give it a random displacement.

3. Calculate the energy of the new configuration and the corresponding number proportional to the probability, that is, $exp\left(-\frac{E_i}{kT}\right)$. Store the values in two separate arrays.

4. Repeat steps 2 and 3 until equilibrium is reached or at least $>10^5$ MCS. One MCS is the number of displacement moves equal to the number of molecules in the system.

5. Calculate $\bar{E} = \sum_{i=1}^{N} p_i E_i$.

The random sampling method takes average over all possible configuration without regard to the value of $exp\left(-\frac{E_i}{kT}\right)$ (the term proportional to probability). Basically, it visits a lot of configurations which have negligible probability of occurrence. These configurations are like those that involve overlaps, clustering of molecules in a particular region (s) of the system etc. Therefore, the technique is computationally extremely costly. But it is completely ergodic.

Trial Moves

A perfectly acceptable method for creating a trial displacement is to add random numbers between $-\Delta/2$ and $+\Delta/2$ to the $x, y,$ and z coordinates of the molecular center of mass:

$$x_i' \rightarrow x_i + \Delta\,(\text{Ranf} - 0.5)$$
$$y_i' \rightarrow y_i + \Delta\,(\text{Ranf} - 0.5)$$
$$z_i' \rightarrow z_i + \Delta\,(\text{Ranf} - 0.5),$$

where Ranf are random numbers uniformly distributed between 0 and 1. Clearly, the reverse trial move is equally probable (hence, α is symmetric).[6]
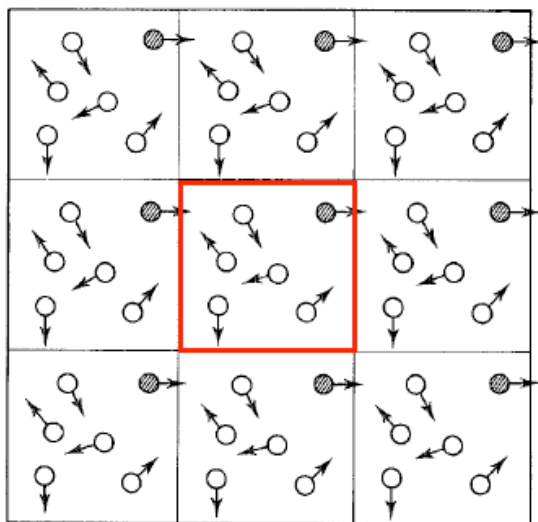
A move could take a molecule outside the simulation box leading to loss of molecules from the system. Another issue is that volume α L^3 but surface of the system increases by L^2. That is, increase in size of the system increases the number of molecules in its volume or bulk faster than the number of molecules on the surface (increases only by L^2). Basically, for a macroscopic system (Avagadro's number) the number of molecules on the surface is negligible compared to that in its bulk. But the simulation box contains much smaller number of molecules ($<10^6$) than the Avagadro's number. Therefore, the surface effects are much more prominent in such a simulation cell compared to a real system. The molecules on the surface have interaction with molecules only from the inside (bulk) of the system. Hence, surface effect in a relatively smaller simulation box is much more than that in real systems.

Periodic boundary conditions gives a solution to this problem.

size of a MD system ~ 10^3-10^5 particles << 10^{23} ⇒ strong boundary effects

Periodic boundary conditions (PBC): it enable a simulation to be performed using a relatively small number of particles in such a way that the particles experience forces as if they were in the bulk fluid

The original box is replicated in all directions to give a periodic array.

Should a particle leave the box during the simulation then it is replaced by an image particle that enters from the opposite side. The number of particles in the central box remains constant.

The coordinates of the particles in the images boxes can be computed by adding or subtracting integral multiples of the box side

replicas of a 2D box of particles

Therefore, periodic boundary is a clever trick to make a simulation that consists of only a few hundred atoms behave as if it was infinite in size. The main reason this is required is to remove the effects of the surface, which any finite sample of matter must have, and which ensure that the internal structure of the sample is dominated by surface rather than bulk forces (like surface

tension - recall how a small drop of water tries to assume a spherical shape, in such cases the surface forces overwhelm the structure of the bulk liquid).

Consult your class notes for understanding the role of mirror image systems in calculation of interaction potential due to molecules on the surface of the central simulation cell.

Why only potential energy is calculated in Monte Carlo simulations?

The canonical partition function is written as:

$$Q = \sum_i \exp\left(-\frac{E_i^*}{k_B T}\right)$$

the first thing to note is that all points in phase space contribute to the sum, and the summation has to be replaced by an integral. For an ideal monatomic gas the expression becomes

$$Q = \frac{1}{N!} \frac{1}{h^{3N}} \int \int \exp\left(-\frac{E}{k_B T}\right) d\mathbf{p} d\mathbf{q}$$

The equation is often written with the Hamiltonian H replacing E, for the reasons discussed above.

The $N!$ term is needed in situations where the particles are completely indistinguishable from one another; for particles that can be distinguished there is no $N!$ term. The integrals have to be done over the spatial variables of all the N particles, and also the momentum variables of the N particles. The integral is therefore a $6N$-dimensional one.

The energy (the Hamiltonian) is always expressible as a sum of kinetic and potential energies, and I have written the mass of each particle m:

$$E = \sum_{i=1}^{N} \frac{p_i^2}{2m} + \Phi(\mathbf{q}_1, \mathbf{q}_2, \ldots, \mathbf{q}_N)$$

Kinetic energies depend on the momentum coordinates $\mathbf{p}$. All the potential energies we will meet depend on the spatial coordinates $\mathbf{q}$ but not on the momenta and so the partition function can be factorized into a product of a kinetic part and a potential part:

$$Q = \frac{1}{N!} \frac{1}{h^{3N}} \int \exp\left(-\frac{1}{k_B T} \sum_{i=1}^{N} \frac{p_i^2}{2m}\right) d\mathbf{p} \int \exp\left(-\frac{\Phi}{k_B T}\right) d\mathbf{q}$$

The kinetic integral has to be done over the momentum coordinates of all N particles, and it can be seen to be a product of N identical three-dimensional integrals of the type

$$\int \exp\left(-\frac{1}{k_B T}\frac{p_1^2}{2m}\right) d\mathbf{p}_1$$

Each of these is a product of three identical standard integrals of the type

$$\int \exp\left(-\frac{1}{k_B T}\frac{p_x^2}{2m}\right) dp_x$$

and the final result is

$$Q = \frac{1}{N!}\left(\frac{2\pi m k_B T}{h^2}\right)^{3N/2}\int \exp\left(-\frac{\Phi}{k_B T}\right) d\mathbf{q}$$

The $3N$-dimensional integral over the position variables is often referred to as the *configurational integral*. For an ideal gas $\Phi = 0$ and so the configurational integral is V^N, where V is the volume of the container. Some authors include $N!$ in the definition of the configurational integral.

The canonical partition function for an ideal gas is therefore

$$Q = \frac{V^N}{N!}\left(\frac{2\pi m k_B T}{h^2}\right)^{3N/2}$$

The partition function for a real system is often written as the product of an ideal part and an excess part due to nonideal behaviour:

$$Q = Q^{\text{ideal}}Q^{\text{excess}} \quad \text{where}$$

$$Q^{\text{excess}} = \frac{1}{V^N}\int \exp\left(-\frac{\Phi}{k_B T}\right) d\mathbf{q}$$

The point of doing this is that thermodynamic properties such as A are often measured experimentally as an ideal and an excess part:

$$A = A^{\text{ideal}} + A^{\text{excess}}$$

The ideal part can be related to Q^{ideal} and the excess part to Q^{excess}.

Thus, in a Monte Carlo simulation only the potential energy part is calculated.

Let us consider a system of monatomic noble gas molecules (like He, Ar etc.)

Such a system experiences only Van der waal interactions.

How to calculate the Van der Waal potential energy?

The Lennard-Jones Pairwise Potential is a model for calculating the non-bonded Van der Waals potential energy of the system. Therefore, to introduce the subject, we choose a system of noble gas monatomic molecules like Ar, Kr etc. that interact among themselves through only pairwise Van der Waals non-bonded potential. The figure below describes the mathematical form of LJ potential. Here 'R' is the centre to centre interatomic distance and σ is the distance where the LJ potential for a given atom type is zero. That is, the curve crosses the x-axis. The energy corresponding to the minimum of the curve is denoted by ϵ. Note that the LJ potential is an empirical model.
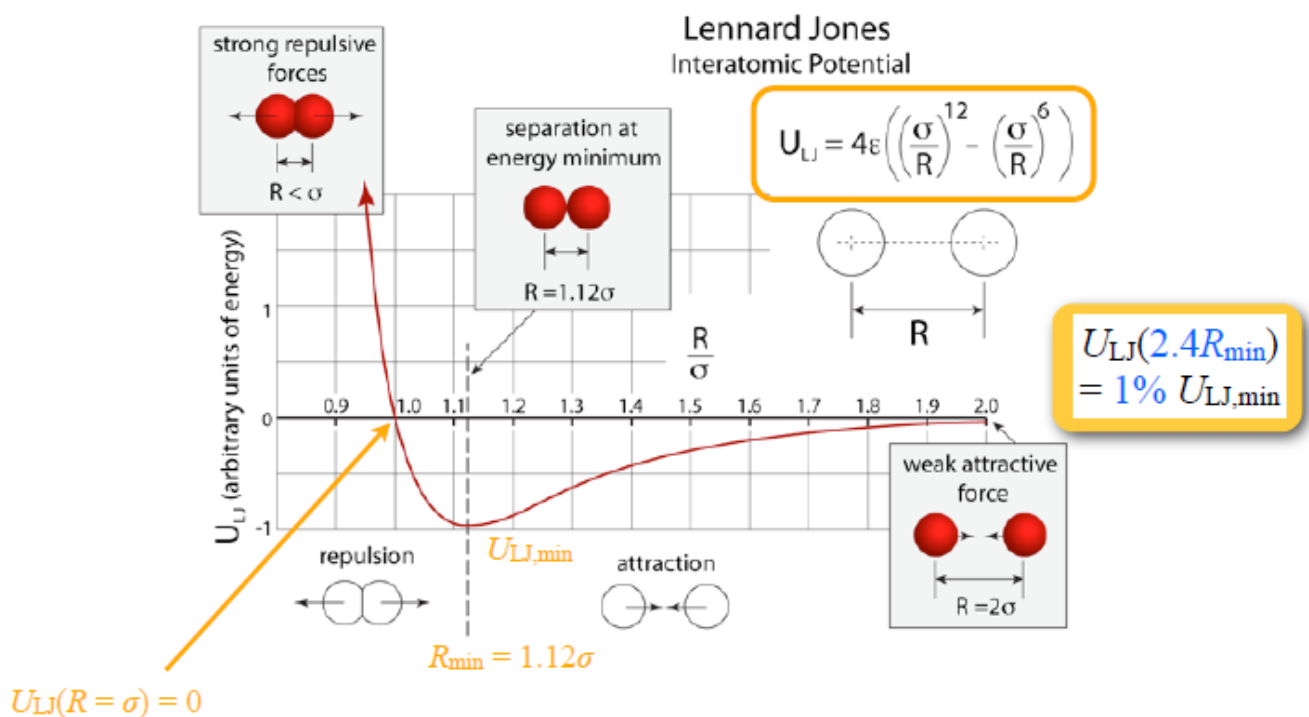
The LJ potential curve asymptotically tends to zero, that is $U_{LJ} \rightarrow 0$ with increase in R. However, the contribution to U_{LJ} becomes very small at $R \geq 2.5\sigma$. The computational cost is reduced by truncating the potential to $2.5\sigma \geq R \geq 3.0\sigma$. That is, the energy of only those pair distances that are within the above range are calculated. There are various cut-off or potential truncation models.

There are several ways to truncate potentials in a simulation. Although the methods are designed to yield similar results, it should be realized that they yield results that may differ significantly, in particular in the vicinity of critical points [51–53] (see Figure 3.3). Often used methods to truncate the potential are

1. Simple truncation

2. Truncation and shift

Simple Truncation   The simplest method to truncate potentials is to ignore all interaction beyond r_c, the potential that is simulated is

$$u^{\text{trunc}}(r) = \begin{cases} u^{lj}(r) & r \leq r_c \\ 0 & r > r_c \end{cases} . \qquad (3.2.6)$$

As already explained, this may result in an appreciable error in our estimate of the potential energy of the true Lennard-Jones potential (3.2.3). Moreover, as the potential changes discontinuously at r_c, a truncated potential is not particularly suitable for a Molecular Dynamics simulation. It can, however, be used in Monte Carlo simulations. In that case, one should be aware that there is an "impulsive" contribution to the pressure due to the discontinuous change of the potential at r_c. That contribution can by no means be ignored.

Truncated and Shifted   In Molecular Dynamics simulations, it is common to use another procedure: the potential is truncated and shifted, such that the potential vanishes at the cutoff radius:

$$u^{\text{tr}-\text{sh}}(r) = \begin{cases} u^{lj}(r) - u^{lj}(r_c) & r \leq r_c \\ 0 & r > r_c \end{cases} . \qquad (3.2.9)$$

In this case, there are no discontinuities in the intermolecular potential and hence no impulsive corrections to the pressure. The advantage of using such a truncated and shifted potential is that the intermolecular forces are always finite.[4] This is important because impulsive forces cannot be handled in those Molecular Dynamics algorithms to integrate the equations of motion that are based on a Taylor expansion of the particle positions. Of course, the potential energy and pressure of a system with a truncated and shifted potential differ from the corresponding properties of both the models with untruncated and with truncated but unshifted pair potentials. But,
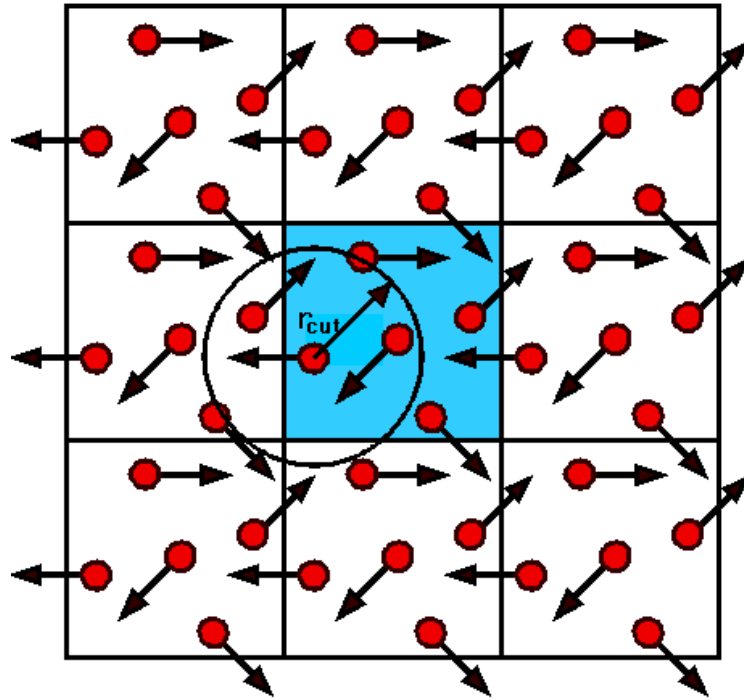
In the above figure r_{cut} is the cutoff radius that is normally applied when calculating the force between two atoms. As you can see, an atom may interact with one in the neighbouring cell (which is an image of one of the atoms in the simulation cell) because it is within the cutoff radius. It ignores the equivalent atom in the simulation cell because it is too far away. In other cases the interaction comes from an atom in the simulation cell itself. Thus the interaction that is calculated is always with the closest image. This is known as the **minimum image** convention.

Note that the cutoff radius is always chosen so that an atom can interact with **only one image** of any given atom. This means that r_{cut} cannot be greater than half the width of the cell.

Reduced Units

In simulations it is often convenient to express quantities such as temperature, density, pressure, and the like in reduced units. This means that we choose a convenient unit of energy, length and mass and then express all

other quantities in terms of these basic units. In the example of a Lennard-Jones system, we use a pair potential that is of the form $u(r) = \epsilon f(r/\sigma)$ (see equation (3.2.3)). A natural (though not unique) choice for our basic units is the following:

- Unit of length, σ

- Unit of energy, ϵ

- Unit of mass, m (the mass of the atoms in the system)

and from these basic units, all other units follow. For instance, our unit of time is

$$\sigma\sqrt{m/\epsilon}$$

and the unit of temperature is

$$\epsilon/k_B.$$

In terms of these reduced units, denoted with superscript *, the reduced pair potential $u^* \equiv u/\epsilon$ is a dimensionless function of the reduced distance $r^* \equiv r/\sigma$. For instance, the reduced form for the Lennard-Jones potential is

$$u^{*lj}(r^*) = 4\left[\left(\frac{1}{r^*}\right)^{12} - \left(\frac{1}{r^*}\right)^6\right]$$

With these conventions we can define the following reduced units: the potential energy $U^* = U\epsilon^{-1}$, the pressure $P^* = P\sigma^3\epsilon^{-1}$, the density $\rho^* = \rho\sigma^3$, and the temperature $T^* = k_B T\epsilon^{-1}$.

One may wonder why it is convenient to introduce reduced units. The most important reason is that (infinitely) many combinations of ρ, T, ϵ, and σ all correspond to the same state in reduced units. This is the law of corresponding states: the same simulation of a Lennard-Jones model can be used to study Ar at 60 K and a density of 840 kg/m^3 and Xe at 112 K and a density of 1617 kg/m^3. In reduced units, both simulations correspond to the state point $\rho^* = 0.5$, $T^* = 0.5$. If we had not used reduced units, we might have

easily missed the equivalence of these two simulations. Another, practical, reason for using reduced units is the following: when we work with real (SI) units, we find that the absolute numerical values of the quantities that we are computing (e.g., the average energy of a particle or its acceleration) are

either much less or much larger than 1. If we multiply several such quantities using standard floating-point multiplication, we face a distinct risk that,

at some stage, we will obtain a result that creates an overflow or under-flow. Conversely, in reduced units, almost all quantities of interest are of order 1 (say, between 10^{-3} and 10^3). Hence, if we suddenly find a very large (or very small) number in our simulations (say, 10^{42}), then there is a good chance that we have made an error somewhere. In other words, reduced

Quantity	Reduced units		Real units
temperature	$T^* = 1$	$\leftrightarrow$	$T = 119.8$ K
density	$\rho^* = 1.0$	$\leftrightarrow$	$\rho = 1680$ kg/m^3
time	$\Delta t^* = 0.005$	$\leftrightarrow$	$\Delta t = 1.09 \times 10^{-14}$ s
pressure	$P^* = 1$	$\leftrightarrow$	$P = 41.9$ MPa

units make it easier to spot errors. Simulation results that are obtained in reduced units can always be translated back into real units. For instance, if we wish to compare the results of a simulation on a Lennard-Jones model at $T^* = 1$ and $P^* = 1$ with experimental data for argon ($\epsilon/k_B = 119.8$ K, $\sigma = 3.405 \times 10^{-10}$ m, $M = 0.03994$ kg/mol), then we can use the translation

Reduced Units

Unit of length is σ. Thus, divide r by σ. Hence reduced length $r^* = r/\sigma$.

Unit of energy is $\in$. Hence, reduced potential energy $U^* = U/\in$.

Unit of mass is m. Divide by actual mass of the atom.

Unit of temperature is $\in/k_B$.

Unit of time is $\sigma\sqrt{m/\epsilon}$.

Unit of Pressure P* $= P\sigma^3/\epsilon$. Characteristic energy is $\epsilon = $ F.$\sigma = (F/\sigma^2).\sigma^3 = P.\sigma^3$.

Therefore characteristic pressure $P = \epsilon / \sigma^3$. Reduced pressure is actual pressure divided by characteristic pressure.

Dimensionless Density $\rho^* = \rho\sigma^3$.

The same simulation of a LJ model can be used to study Ar at 60K and density of 840 Kg/m^3 and Xe at 112K and density of 1617 Kg/m^3. In reduced units both simulations correspond to $\rho^* = 0.5$ and T* $= 0.5$.

Importance sampling Monte Carlo or the Metropolis algorithm

As mentioned earlier, random sampling finds the value of the concerned observable (example energy, pressure etc. are observables) at random phase space points (or molecular configurations). The technique spends (or wastes) a lot of computation time in finding the values of configurations that have extremely low probability of occurrence. Obviously, the averages are poor, that is, they show a lot of deviation from the true average value.

Consequently, for efficient computation of the ensemble average, we need to devise a technique that will find the observable value for configurations of the system that have a finite value of occurrence. The trick is to only generate configurations that have a finite value of occurrence. To implement this, we start by generating the initial configuration of the system such that its probability of occurrence is finite (or a non-vanishing Boltzmann factor $e^{-\frac{E_i}{kT}}$). A simple solution is to ensure that in the initial configuration there is no overlap between molecules for a system of given density of molecules. Let this configuration be denoted by o. Pick a random molecule in the system and give it a displacement. We call this configuration as n. Let the probability of occurrence of configuration o be $P(o)$ and $P(n)$ be the probability of occurrence of configuration n of the system. If the $\pi(o \rightarrow n)$ is the probability of transition from o to n and $\pi(n \rightarrow o)$ is the transition probability of n to o then the following the principle of detailed balance must hold to ensure that once the system reaches equilibrium then it cannot leave it.

$$P(o)\pi(o \rightarrow n) = P(n)\pi(n \rightarrow o) \qquad (1)$$

A Monte Carlo move consists of two stages. In the first stage a molecule in the system is selected randomly and given a random displacement. This is known as the $\alpha(o \rightarrow n)$ transition matrix. The second step is to accept or reject the move and is denoted by $acc(o \rightarrow n)$. In detailed balance condition the transition matrix $\alpha(o \rightarrow n)$ is completely symmetric. That is, $\alpha(o \rightarrow n) = \alpha(n \rightarrow o)$. This means that since the selection of a molecule is random, therefore, there is equal chance of the same molecule being selected in the subsequent move. Hence,

$$\pi(o \rightarrow n) = \alpha(o \rightarrow n) \times acc(o \rightarrow n) \tag{2}$$

Since $\alpha(o \rightarrow n) = \alpha(n \rightarrow o)$, therefore,

$$P(o)\alpha(o \rightarrow n) \times acc(o \rightarrow n) = P(n)\alpha(n \rightarrow o) \times acc(n \rightarrow o) \tag{3}$$

Hence, $P(o) \times acc(o \rightarrow n) = P(n) \times acc(n \rightarrow o) \tag{4}$

$$\frac{acc(o \rightarrow n)}{acc(n \rightarrow o)} = \frac{P(n)}{P(o)} = \exp\left\{-\frac{1}{kT}(E_n - E_o)\right\} \tag{5}$$

Note the probability $acc(o \rightarrow n)$ cannot be greater than 1. Following is the probability choice of Metropolis.

$$acc(o \rightarrow n) = \frac{P(n)}{P(o)} \quad \text{if} \qquad P(n) < P(o) \tag{6a}$$

$$acc(o \rightarrow n) = 1 \quad \text{if} \qquad P(n) \geq P(o) \tag{6b}$$

See the detailed step by step Metropolis algorithm from the class notes.

Molecular Dynamics Simulations

MD simulations are similar to real experiments where we measure the property of interest over a time interval. Thus, in MD we take a long time average such that each such average is reproduced over a similar time interval. The first part is identical to MC simulations. We construct the initial configuration of the system containing N molecules. To make things easier to understand we take the same MC example. Thus, the monoatomic molecules are arranged in a non-overlapping regular array arrangement. As mentioned earlier, this is necessary to ensure that the initial configuration has a finite probability of occurrence in its phase space. In other words, its exp(-E_i/kT) factor is a finite number. Such a starting point ensures that the system mostly equilibrates to the nearest minima in the respective potential energy surface space.

In contrast to MC there is no mechanism for the system to fluctuate to a configuration near another minima. We solve the Newton's laws of motions for this system until its time average properties do not show any change with time. This part of the simulation is called equilibration. The time average properties are measured in a subsequent long

interval called the production run. Hence, it is critical to ensure that the time average is truly over a long interval and is reproduced over similar such intervals.

A Simple MD program

Step 1 Input the initial parameters: a) initial density and number of molecules, b) Time step, c) initial temperature.

Step 2 Assign initial positions of the molecules (with respect to position of the molecules) as per chosen density. Also assign velocities to the molecules such that the system has the desired initial temperature.

Step 3 Compute forces on all molecules in the system. The force on each molecule is the resultant of the vector sum of forces due to N – 1 interactions with the rest of the molecules in the system.

Step 4 Integrate Newton's equations of motion to find the position of a molecule in the next time instant using the resultant force due to rest of the N -1 molecules. Likewise, calculate the positions of the rest of the molecules in the next time instant. Note, we calculate the positions of all molecules in the next time instant of the system simultaneously.

Step 5 Steps 3 and 4 are computed iteratively until the desired time evolution (or time steps) is complete.

Step 6 Print time averages of the desired quantities.

The initial inputs are the position and the momenta of all molecules making the system.

Assignment of velocities and temperature of the system:

The position of the system's N particles are specified by a N set of vectors at time, t. Total Energy ($E = K+U$) is the sum of Kinetic (K) and Potential (U) Energies. Here

$$K = \frac{1}{2}m_i \sum_{i=1}^{N} v_i^2$$

Assignment of initial velocities is based on the **equipartition theorem**:

The total kinetic energy of a system, K, is shared equally amongst all energetically accessible degrees of freedom of a system. ($\Longleftrightarrow$ **2nd law of thermodynamics**). Each molecule has 3 translational degrees of freedom.

• It further states that each quadratic degree of freedom will, on average, possess an energy $(1/2)k_B T$. A 'quadratic degree of freedom' is one for which the energy depends on the square of some property.

• Thus the following relation should hold in thermal equilibrium: In a classical definition of temperature it is computed as the average kinetic energy per degree of freedom, f. The equation below is the operational definition of temperature.

$$\frac{1}{2}k_B T = \left\langle \frac{1}{2}mv^2 \right\rangle \qquad \qquad k_B T = \frac{\langle 2K \rangle}{f}$$

In a simulation, we use this equation as an operational definition of the temperature. In practice, we would measure the total kinetic energy of the system and divide this by the number of degrees of freedom N_f (= $3N - 3$ for a system of N particles with fixed total momentum[1]). As the total kinetic energy of a system fluctuates, so does the instantaneous temperature:

$$T(t) = \sum_{i=1}^{N} \frac{m_i v_i^2(t)}{k_B N_f}. \qquad (4.1.2)$$

The relative fluctuations in the temperature will be of order $1/\sqrt{N_f}$. As N_f is typically on the order of 10^2–10^3, the statistical fluctuations in the temperature are on the order of 5–10%. To get an accurate estimate of the temperature, one should average over many fluctuations.

To assign initial velocities to the molecules take them randomly from a Maxwell-Boltzmann distribution at the temperature of interest.

$$p(v_{ix}) = \left(\frac{m_i}{2\pi k_B T} \right)^{1/2} \exp \left[-\frac{1}{2}\frac{m_i v_{ix}^2}{k_B T} \right]$$

The Maxwell-Boltzmann equation gives the distribution that an atom I of mass m, has a velocity v_{ix} in the x direction at a temperature. A Maxwell-Boltzmann distribution is a Gaussian distribution. A random number generator produces numbers uniformly in the interval 0 and 1. Then this uniform distribution is converted into a Gaussian distribution. The initial velocities are then adjusted so that the total momentum of the system is zero.

Force Calculation

This step is the most time consuming part of an MD simulation. As mentioned earlier, we have to consider the force on particle i due to interactions with all its neighbours.

The time needed for evaluation of forces scales as N^2 (since number of interactions is $N(N-1)/2$).

If a given pair of particles is close enough to interact, we must compute the force between these particles, and the contribution to the potential energy. Suppose that we wish to compute the x-component of the force

$$f_x(r) = -\frac{\partial u(r)}{\partial x}$$
$$= -\left(\frac{x}{r}\right)\left(\frac{\partial u(r)}{\partial r}\right).$$

For a Lennard-Jones system (in reduced units),

$$f_x(r) = \frac{48x}{r^2}\left(\frac{1}{r^{12}} - 0.5\frac{1}{r^6}\right).$$

Integration Algorithms

Finite difference techniques are used to generate molecular dynamics trajectories with continuous potential models, which we will assume to be pairwise additive. The essential idea is that the integration is broken down into many small stages, each separated in time by a fixed time δt. The total force on each particle in the configuration at a time t is calculated as the vector sum of its interactions with other particles. From the force we can determine the accelerations of the particles, which are then combined with the positions and velocities at a time t to calculate the positions and velocities at a time $t + \delta t$. The force is assumed to be constant during the time step. The forces on the particles in their new positions are then determined, leading to new positions and velocities at time $t + 2\delta t$, and so on.

There are many algorithms for integrating the equations of motion using finite difference methods, several of which are commonly used in molecular dynamics calculations. All algorithms assume that the positions and dynamic properties (velocities, accelerations, etc.) can be approximated as Taylor series expansions:

$$r(t + \delta t) = r(t) + \delta t v(t) + \tfrac{1}{2}\delta t^2 a(t) + \tfrac{1}{6}\delta t^3 b(t) + \tfrac{1}{24}\delta t^4 c(t) + \cdots \tag{7.2}$$

$$v(t + \delta t) = v(t) + \delta t a(t) + \tfrac{1}{2}\delta t^2 b(t) + \tfrac{1}{6}\delta t^3 c(t) + \cdots \tag{7.3}$$

$$a(t + \delta t) = a(t) + \delta t b(t) + \tfrac{1}{2}\delta t^2 c(t) \cdots \tag{7.4}$$

$$b(t + \delta t) = b(t) + \delta t c(t) + \cdots \tag{7.5}$$

where v is the velocity (the first derivative of the positions with respect to time), a is the

Acceleration, and b is the third derivative with respect to time.

The most commonly used algorithm for time integration in MD is the Verlet algorithm. For starting the integration of the Newton's equations of motions in this algorithm we need to know the positions of all particles at the present r(t) and the

previous time instant (r(t-Δt)). While the positions of all molecules in the present instant are known to us, the approximate positions of molecules in the previous time instant are found by x(t- Δt) = x (t) –v. Δt. The only consideration in this approximate method is the conservation of linear momentum.

$$r(t + \Delta t) = r(t) + v(t)\Delta t + \frac{f(t)}{2m}\Delta t^2 + \frac{\Delta t^3}{3!}\dddot{r} + O(\Delta t^4) \qquad (1)$$

Similarly

$$r(t - \Delta t) = r(t) - v(t)\Delta t + \frac{f(t)}{2m}\Delta t^2 - \frac{\Delta t^3}{3!}\dddot{r} + O(\Delta t^4) \qquad (2)$$

Adding equations (1) and (2) we get:

$$r(t + \Delta t) = 2r(t) - r(t - \Delta t) + \frac{f(t)}{m}\Delta t^2 + 2O(\Delta t^4) \qquad (3)$$

We neglect the calculation of the last term since it is quite small compared to other terms. Note this does introduce a small error.

$$r(t + \Delta t) = 2r(t) - r(t - \Delta t) + \frac{f(t)}{m}\Delta t^2 \qquad (4)$$

Verlet algorithm does not use velocity to calculate the new positions. Velocities are computed by using the following expression:

$$r(t + \Delta t) - r(t - \Delta t) = 2v(t)\Delta t + 2\frac{\Delta t^3}{3!}\dddot{r} \qquad (5)$$

$$v(t) = \frac{r(t+\Delta t)-r(t-\Delta t)}{2\Delta t} + O(\Delta t^2) \qquad (6)$$

The expression of velocity is, therefore, accurate only to the order of $O(\Delta t^2)$. Now that we have computed the new positions, we discard the positions at time $(t - \Delta t)$. The current positions become the old positions and the new positions become the current positions.

After each time step we compute the current temperature, current potential energy, and total energy. Note that total energy must remain conserved.

After commencing a molecular dynamics simulation an **equilibration period** is necessary, usually lasting a few thousand time steps. During this period the system is coaxed towards the desired thermodynamic state point (defined by temperature and density) by a technique known as temperature scaling. After a sufficient equilibration period the system settles down to the desired condition. Then a **production period** begins in which the trajectory (or history) of the molecules is stored for later analysis. Many thousands of time steps (perhaps millions) may be needed to derive a statistically accurate description of the phenomenon of interest. The process

by which properties of the bulk material are drawn out of the mass of trajectory data is known as <u>ensemble averaging</u>.

Points to be noted in the Verlet algorithm:

• The expression for v(t) is only accurate to order $O(\Delta t^2)$. Truncation error.

• Note that the kinetic energy and thus instantaneous temperatures at time t cannot be calculated until the positions are known at time $t + \Delta t$. While the velocities are not needed immediately for calculation of the future instant positions, they are required to compute the kinetic energy of the system. The latter is necessary for knowing whether total energy (KE + PE) was conserved during the time step or not.

• This deficiency can either be dealt with using the Leap Frog or Velocity Verlet algorithm.

• Note that the total energy should be conserved (NVE ensemble).

Criteria for a good algorithm to integrate Newton's equations of motion:

1. **Speed** is **not important** since most time is spent on calculating non-bonded interactions and forces rather than integrating the equations of motion.

Verlet Algorithm (VA): Fast, but relatively unimportant.

2. **Accuracy** for large time steps. The longer the time step, the fewer evaluations of the energies and forces are needed.

VA: Not very accurate for long time steps, i.e., only short time steps ($\Delta t = 1$ fs) possible.

3. **Energy conservation** is an important criterion where one has to distinguish between short-time and long-time energy conservation.

In general, one comes at the cost of the other.

VA: The short-term energy conservation is fair and, more important, it exhibits little long-term energy drift.

4. Newton's equations of motion are **time reversible**, and so should be the integration algorithms. Non-reversible algorithms will have serious long-term energy drift problems.

VA: Is time reversible (related to its little long-term energy drift).

Molecular Dynamics Simulations: Limitations

Force Field Dependency:

• The results of a MD simulation can only be as good as the underlying force field.

Neglect of Electronic Motion:

• Only the nuclear motion is followed in classical MD.

• Electronic motion is not considered and quantum effects are generally ignored.

• Classical MD is thus unsuitable for chemical reactions and chemical bonding of metal ions. Quantum dynamical approaches are used for this purpose.

Critical frequencies:

• Classical MD is also unsuitable for low temperatures where quantum effects are more pronounced.

• In general: Whenever $h\vartheta > k_B T$, we should worry about quantum effects.

Let us now briefly look at some alternatives to the Verlet algorithm. The most naive algorithm is based simply on a truncated Taylor expansion of the particle coordinates:

$$r(t + \Delta t) = r(t) + v(t)\Delta t + \frac{f(t)}{2m}\Delta t^2 + \cdots .$$

If we truncate this expansion beyond the term in Δt^2, we obtain the so-called Euler algorithm. Although it looks similar to the Verlet algorithm, it is much worse on virtually all counts. In particular, it is not reversible or area preserving and suffers from a (catastrophic) energy drift. The Euler algorithm therefore is not recommended.

Several algorithms are equivalent to the Verlet scheme. The simplest among these is the so-called Leap Frog algorithm [24]. This algorithm evaluates the velocities at half-integer time steps and uses these velocities to compute the new positions. To derive the Leap Frog algorithm from the Verlet scheme, we start by defining the velocities at half-integer time steps as follows:

$$v(t - \Delta t/2) \equiv \frac{r(t) - r(t - \Delta t)}{\Delta t}$$

and

$$v(t + \Delta t/2) \equiv \frac{r(t + \Delta t) - r(t)}{\Delta t}.$$

From the latter equation we immediately obtain an expression for the new positions, based on the old positions and velocities:

$$r(t + \Delta t) = r(t) + \Delta t v(t + \Delta t/2). \tag{4.3.1}$$

From the Verlet algorithm, we get the following expression for the update of the velocities:

$$v(t + \Delta t/2) = v(t - \Delta t/2) + \Delta t \frac{f(t)}{m}. \tag{4.3.2}$$

As the Leap Frog algorithm is derived from the Verlet algorithm, it gives rise to identical trajectories. Note, however, that the velocities are not defined at the same time as the positions. As a consequence, kinetic and potential energy are also not defined at the same time, and hence we cannot directly compute the total energy in the Leap Frog scheme.

It is, however, possible to cast the Verlet algorithm in a form that uses positions and velocities computed at equal times. This velocity Verlet algorithm [69] looks like a Taylor expansion for the coordinates:

$$r(t + \Delta t) = r(t) + v(t)\Delta t + \frac{f(t)}{2m}\Delta t^2. \tag{4.3.3}$$

However, the update of the velocities is different from the Euler scheme:

$$v(t + \Delta t) = v(t) + \frac{f(t + \Delta t) + f(t)}{2m}\Delta t. \tag{4.3.4}$$

Note that, in this algorithm, we can compute the new velocities only after we have computed the new positions and, from these, the new forces. It is not

immediately obvious that this scheme, indeed, is equivalent to the original Verlet algorithm. To show this, we note that

$$r(t + 2\Delta t) = r(t + \Delta t) + v(t + \Delta t)\Delta t + \frac{f(t + \Delta t)}{2m}\Delta t^2$$

and equation (4.3.3) can be written as

$$r(t) = r(t + \Delta t) - v(t)\Delta t - \frac{f(t)}{2m}\Delta t^2.$$

By addition we get

$$r(t + 2\Delta t) + r(t) = 2r(t + \Delta t) + [v(t + \Delta t) - v(t)]\Delta t + \frac{f(t + \Delta t) - f(t)}{2m}\Delta t^2.$$

Substitution of equation (4.3.4) yields

$$r(t + 2\Delta t) + r(t) = 2r(t + \Delta t) + \frac{f(t + \Delta t)}{m}\Delta t^2,$$

which, indeed, is the coordinate version of the Verlet algorithm.

What ensemble is MD? An energy-conserving trajectory gives results for a microcanonical (N,V,E) ensemble (i.e., fixed N, volume, and total energy).

More typically, we are interested in a thermal ensemble, such as the canonical (N,V,T) ensemble (fixed N, volume, and temperature):

$p(r) \propto \exp(-U(r)/k_BT)$ Boltzmann distribution

Unfortunately, the microcanonical ensemble does not correspond to the conditions under which most experiments are carried out. If one is interested in the behavior of the system at a specific temperature, a NVT simulation using a thermostat is required. Another reason to simulate using a thermostat is to avoid steady energy drifts caused by the accumulation of numerical errors during MD simulations. An obvious way to alter the temperature of the system is velocity scaling. If the temperature at time t is T (t) and the velocities are multiplied by a factor λ, then the associated temperature change can be calculated as

$$\Delta T = \frac{1}{2}\sum_{i=1} 2\frac{m_i\,(\lambda v_i)^2}{N_{df}k_B} - \frac{1}{2}\sum_{i=1} 2\frac{m_i v_i^2}{N_{df}k_B} \tag{2}$$

$$\Delta T = \left(\lambda^2 - 1\right) T(t) \tag{3}$$

$$\lambda = \sqrt{T_0/T(t)} \tag{4}$$

The simplest way to control the temperature is thus to multiply the velocities at each time step by the factor λ, where T (t) is the current temperature as calculated from the kinetic energy and T_0 is the desired temperature.

One problem with this approach is, that it does not allow fluctuations in temperature which are present in the canonical ensemble.

Scaling can be done at every time step, or only every few steps..

**Advantage:**

• Straight-forward to code.

Disadvantages:

• Results do not correspond to any ensemble, though in practice, the amount they deviate from canonical is quite small. Not recommended for use in production MD runs because they do not strictly conform to the canonical ensemble, but fine to use during equilibration.

• Does not remove localized or unwanted correlation motion.

• Not time-reversible or deterministic.

Berendsen Thermostat

Another popular velocity scaling thermostat is that of Berendsen. Here, the scaling is given by

$$\frac{dv}{dt} = \frac{f}{m} + \frac{1}{2\tau}\left(\frac{T_{\mathrm{md}}}{T(t)} - 1\right)v$$

τ is called the 'rise time' of the thermostat. It describes the strength of the coupling of the system to a hypothetical heat bath. The larger τ, the weaker the coupling, i.e., the longer it takes to achieve a given T_{md} from the current $T(t)$:
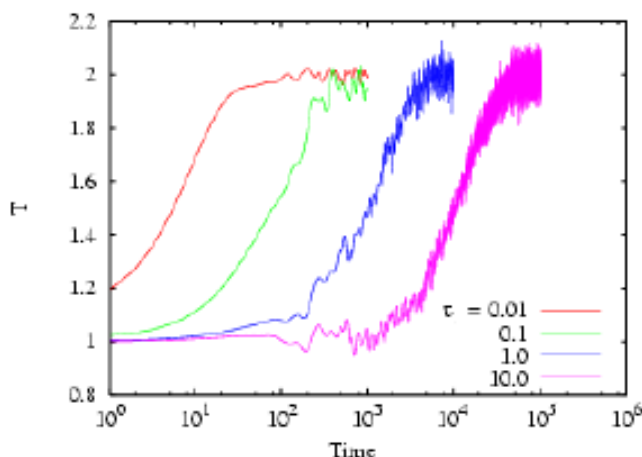
In practice, τ is used as an empirical parameter to adjust the strength of the coupling. Its value has to be chosen with care. In the limit $\tau \to \infty$ the Berendsen thermostat is inactive and the run is sampling a microcanonical ensemble. The temperature fluctuations will grow until they reach the appropriate value of a microcanonical ensemble. However, they will never reach the appropriate value for a canonical ensemble. On the other hand, too small values of τ will cause unrealistically low temperature fluctuations. If τ is chosen the same as the timestep Δt, the Berendsen thermostat is nothing else than the simple velocity scaling. Values of $\tau \approx 0.1$ps are typically used in MD simulations of condensed-phase systems. The ensemble generated when using the Berendsen thermostat is not a canonical ensemble!

Advantages:

• Straight-forward to code.

• Robust.

Disadvantages:

• Results do not correspond to any ensemble, though in practice, the amount they deviate from canonical is quite small. Not recommended for use in production MD runs because they do not strictly conform to the canonical ensemble, but fine to use during equilibration.
• Does not remove localized or unwanted correlation motion.
• Not time-reversible or deterministic.
Berendsen et al, J. Chem. Phys. 81, 3684 (1984).

Nosé-Hoover Thermostat

Add one new variable, s, to equations of motion, and scale momenta by $1/s$. With mass Q and friction coefficient ζ, s acts as a thermal reservoir.

$$H_{\text{Nose-Hoover}} = \sum_{i=1}^{N} \frac{\mathbf{p}_i^2}{2m_i} + U(\mathbf{R}) + \frac{\zeta^2 Q}{2} + (3N)\frac{\ln s}{\beta} \qquad (14)$$

• The logarithmic term $(\ln s)$ is needed to have the correct scaling of time. Any other scheme that does not have such a logarithmic term will fail to describe the canonical ensemble correctly.

• Built on elegant formalism proposed by Nosé (1984), in which microcanonical dynamics on this extended system is shown to give canonical properties.

• The mass Q determines the strength of the thermostat. The choice of Q is critical in the implementation of this thermostat.

• Deterministic and time-reversible.

Thermostats

Thermostat	Brief description	canonical?	stochastic?
Velocity rescaling	E_{kin} fixed to match T_{md}	no	no
Berendsen	E_{kin} fixed to match T_{md}	no	no
Nose-Hoover	extra degree of freedom acts as thermal reservoir	in principle, but caution	no
Nose-Hoover chain	(...(((NH)NH)NH)...)	yes-probably	no
Langevin	noise + frictional drag balances to give correct T	yes	yes
Andersen	occasionally re-randomize momenta	yes	yes

Interaction Potentials

It is not possible to calculate the thermodynamics properties of a large number (explicit) interacting molecules by quantum mechanics. The computational cost is huge. Therefore, the advent of statistical thermodynamics. We talked about how to find the most probable distribution of microstates of a system and how the ensemble average of an observable is equal to its experimental value. But we did not talk about how to calculate the E_i of the 'i'th microstate. Since it is not possible to compute this quantity by quantum mechanics, therefore, we devise interaction potential models for different types of molecular systems. Force field methods/interaction models or molecular mechanics are basically different names of the same technique. These methods basically ignore electronic motion and treat the molecule as collection of nuclei with their energetics dependent on the inter-nuclear motion. Molecular mechanics is a simple model of finding the interaction energy of a system due to the vibrational motion of bonds, opening and closing of angles, rotation about bonds and non-bonded interactions. Thus, various terms are assigned to changes in specific internal coordinates such as bond length, bond angles, and the rotation of bonds and movements of atoms relative to each other. Interaction potentials primarily consist of four terms.

$$\mathscr{V}(\mathbf{r}^N) = \sum_{bonds} \frac{k_i}{2}(l_i - l_{i,0})^2 + \sum_{angles} \frac{k_i}{2}(\theta_i - \theta_{i,0})^2 + \sum_{torsions} \frac{V_n}{2}(1 + \cos(n\omega - \gamma))$$

$$+ \sum_{i=1}^{N} \sum_{j=i+1}^{N} \left(4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \right)$$

$$+ \mathbf{E_{cross}}$$

U($\mathbf{r^N}$) denotes the potential energy of the system as function of the positions of the N atoms making the system. The first term on the right hand side (RHS) models the

interaction between bonded atoms, modelled here by a harmonic potential that increases as the bond length deviates from the equilibrium position. The second term is a summation over all the valence angles in the molecule. A valence angle is the angle formed between C-B-D, where both C and D are bound to B. The third term is the torsional potential that tells how the energy changes with bond rotation. The fourth term takes care of the non-bonded interaction between all pairs of atoms that are in different molecules or that are in the same molecule but separated by at least three bonds. The non-bonded part consists of Coulomb term and van-der Waals terms. Finally, E_{cross} describes the coupling between the first three terms.

Bond stretching

Angle bending

Bond rotation
(torsion)

Non-bonded interactions
(electrostatic)

Non-bonded interactions
(van der Waals)
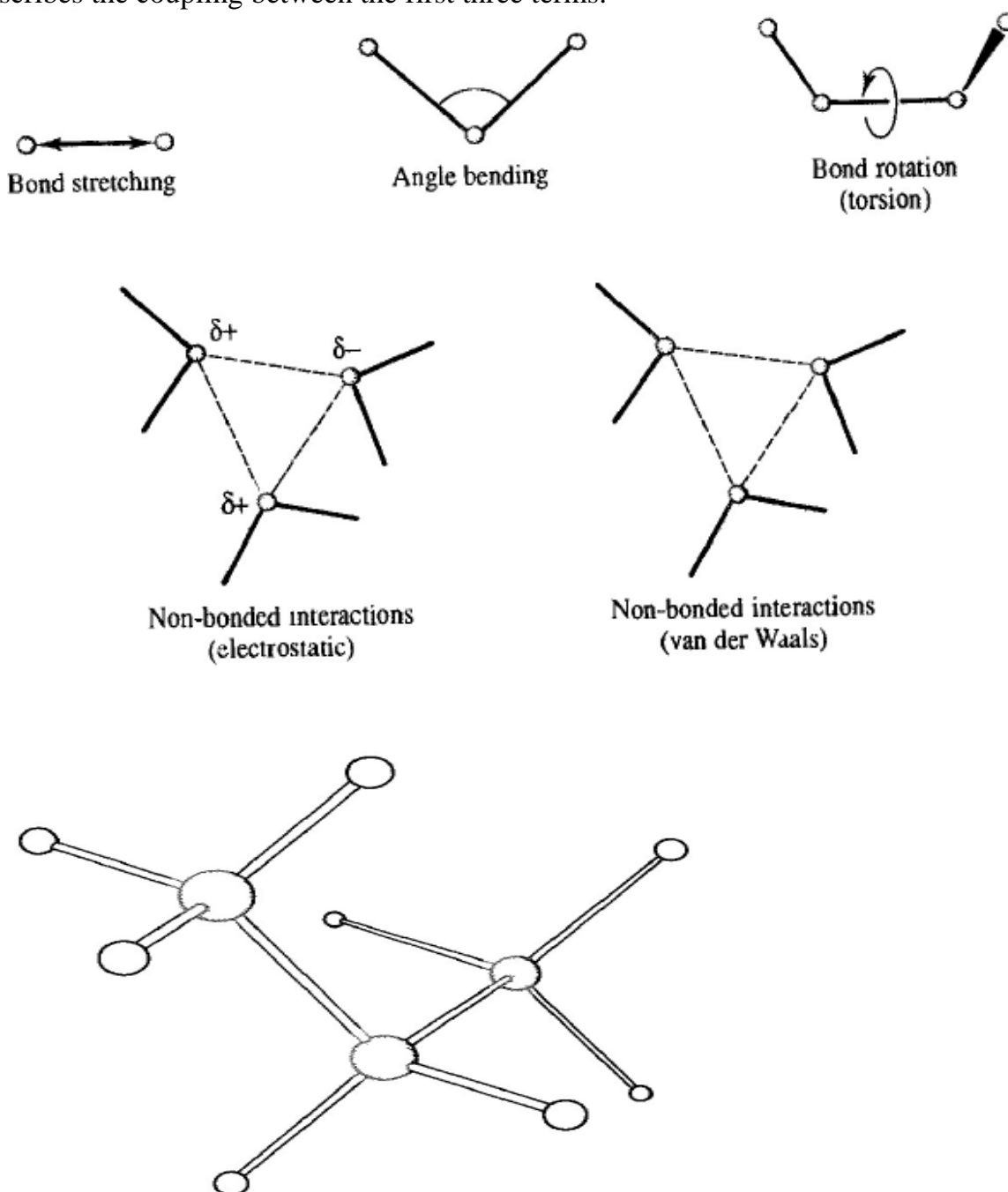
A typical model of propane consists of ten bond stretching terms, eighteen angle bending terms, eighteen torsional terms and 27 non-bonded terms.

Propane has 2 C-C bonds, 8 C-H bonds. The C-C bonds are symmetrically equivalent but there are two types of C-H bonds. One methylene (CH_2) and two methyl groups (six C-H bonds). In most cases the two types of bonds are treated as equivalent.

C−H bonds. This is an example of the way in which the same parameters can be used for a wide variety of molecules. There are 18 different valence angles in propane, comprising one C−C−C angle, ten C−C−H angles and seven H−C−H angles. Note that all angles are included in the force field model even though some of them may not be independent of the others. There are 18 torsional terms: twelve H−C−C−H torsions and six H−C−C−C torsions. Each of these is modelled with a cosine series expansion that has minima at the *trans* and *gauche* conformations. Finally, there are 27 non-bonded terms to calculate, comprising 21 H−H interactions and six H−C interactions. The electrostatic contribution would be calculated using Coulomb's law from partial atomic charges associated with each atom and the van der Waals contribution as a Lennard-Jones potential with appropriate ε_{ij} and σ_{ij} parameters. A sizeable number of terms are thus included in the force field model, even for a molecule as simple as propane. Even so, the number of terms (73) is many fewer than the number of integrals that would be involved in an equivalent *ab initio* quantum mechanical calculation.

Atom types

A concept that is common to most force fields is that of an *atom type*. When preparing the input for a quantum mechanics calculation it is usually necessary to specify the atomic numbers of the nuclei present, together with the geometry of the system and the overall charge and spin multiplicity. For a force field the overall charge and spin multiplicity are not explicitly required, but it is usually necessary to assign an atom type to each atom in the system. The atom type is more than just the atomic number of an atom; it usually contains information about its hybridisation state and sometimes the local environment. For example, it is necessary in most force fields to distinguish between sp^3-hybridised carbon atoms (which adopt a tetrahedral geometry), sp^2-hybridised carbons (which are trigonal) and sp-hybridised carbons (which are linear). Each force field parameter is expressed in terms of these atom types, so that the reference angle θ_0 for a tetrahedral carbon atom would be near 109.5° and that for a trigonal carbon would be near 120°. The atom types in some force fields reflect the neighbouring environment as well as the hybridisation and can be quite extensive for some atoms. For example, the MM2, MM3 and MM4 force fields of Allinger and co-workers that are widely used for calculations on 'small' molecules [Allinger 1977; Allinger *et al.* 1989, 1990a, b, 1996a, b; Lii and Allinger 1989; Nevins *et al.* 1996a, b, c] distinguish the following types of carbon atom: sp^3, sp^2, sp, carbonyl, cyclopropane, radical, cyclopropene and carbonium ion. In the AMBER force field of Kollman and co-workers [Weiner *et al.* 1984; Cornell *et al.* 1995] the carbon atom at the junction between a six- and a five-membered ring (e.g. in the amino acid tryptophan) is assigned

an atom type that is different from the carbon atom in an isolated five-membered ring such as histidine, which in turn is different from the atom type of a carbon atom in a benzene ring. Indeed, the AMBER force field uses different atom types for a histidine amino acid depending upon its protonation state (Figure 4.3). Other, more general, force fields would assign these atoms to the same generic 'sp^2 carbon' atom type. It is often found that force fields which are designed for modelling specific classes of molecule (such as proteins and nucleic acids, in the case of AMBER) use more specific atom types than force fields designed for general-purpose use.

Tryptophan
Phenylalanine
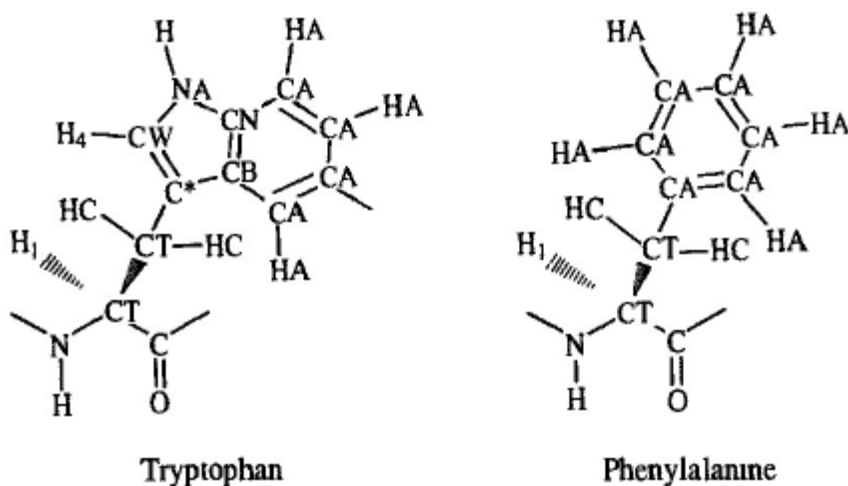
Indeed, one might expect that force constants and equilibrium lengths might vary substantially even when A and B remain constant, but the bond itself is embedded in different molecular frameworks (i.e., surroundings). However, as more and more spectroscopic data became available in the early 20th century, particularly in the area of organic chemistry, where hundreds or thousands of molecules having similar bonds (e.g., C–C single bonds) could be characterized, it became empirically evident that the force constants and equilibrium bond lengths were largely the same from one molecule to the next if the bond type, order and the chemical environment are similar. This phenomenon came to be called 'transferability'.

Concomitant with these developments in spectroscopy, thermochemists were finding that, to a reasonable approximation, molecular enthalpies could be determined as a sum of bond enthalpies. Thus, assuming transferability, if two different molecules were to be composed of identical bonds (i.e., they were to be isomers of one kind or another), the sum of the differences in the 'strains' of those bonds from one molecule to the other (which would arise from different bond lengths in the two molecules – the definition of strain in this instance is the positive deviation from the zero of energy) would allow one to predict the difference in enthalpies. Such prediction was a major goal of the emerging area of organic conformational analysis.

The Bond Stretch

The harmonic form is the simplest possible, and sufficient for determining most equilibrium geometries. There are certain strained and crowded systems where the results from a harmonic approximation are significantly different from experimental values, and if the force field should be able to reproduce features such as vibrational frequencies, the functional form for Estr must be improved. The straightforward approach is to include more terms in the Taylor expansion.

$$E_{\text{str}}(\Delta R^{\text{AB}}) = k_2^{\text{AB}}(\Delta R^{\text{AB}})^2 + k_3^{\text{AB}}(\Delta R^{\text{AB}})^3 + k_4^{\text{AB}}(\Delta R^{\text{AB}})^4 + \cdots$$

This of course has a price: more parameters have to be assigned.

Polynomial expansions of the stretch energy do not have the correct limiting behaviour. The cubic anharmonicity constant $k3$ is normally negative, and if the Taylor expansion is terminated at third order, the energy will go toward $-\infty$ for long bond lengths. minimization of the energy with such an expression can cause the molecule to fly apart if a poor starting geometry is chosen. The quartic constant $k4$ is normally positive and the energy will go toward $+\infty$ for long bond lengths if the Taylor series is terminated at fourth order. The correct limiting behaviour for a bond stretched to infinity is that the energy should converge towards the dissociation energy.
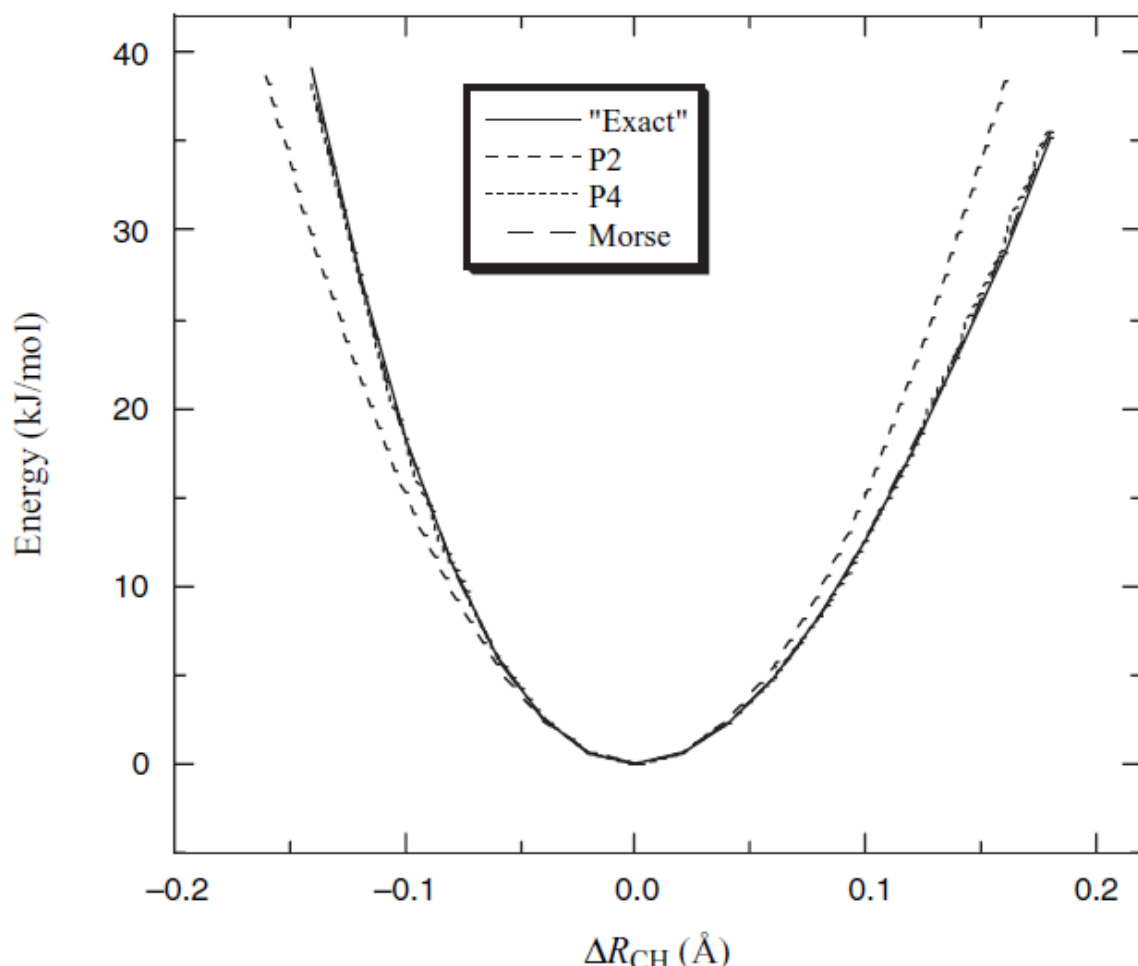
The stretch energy for CH$_4$

Until now, we have used two different words for the R_0 parameter, the "natural" or the "equilibrium" bond length. The latter is slightly misleading. The R_0 parameter is *not* the equilibrium bond length for *any* molecule! Instead it is the parameter which,

when used to calculate the minimum energy structure of a molecule, will produce a geometry having the experimental equilibrium bond length. If there were only one stretch energy in the whole force field energy expression (i.e. a diatomic molecule), R_0 would be the equilibrium bond length. However, in a polyatomic molecule the other terms in the force field energy will usually produce a minimum energy structure with bond lengths slightly longer than R_0. R_0 is the hypothetical bond length if no other terms are included, and the word "natural" bond length is a better description of this parameter than "equilibrium" bond length. Essentially all molecules have bond lengths that deviate very little from their "natural" values, typically by less than 0.03Å. For this reason a simple harmonic is usually sufficient for reproducing experimental geometries.

The van der Waals energy

The van der Waals term is the only interaction between rare gas atoms (and thus the reason why say argon can become a liquid and a solid) and it is the main interaction between non-polar molecules such as alkanes. We have already discussed the Lennard-Jones potential describing this contribution. There are other forms of such non-bonded potential as well. However, in this introductory course we will stick to the LJ pontential. the non-bonded energy.

E_{vdw} may be interpreted as the non-polar part of the interaction not related to electrostatic energy due to (atomic) charges. E_{vdw} is zero at large interatomic distances and becomes very repulsive for short distances. In quantum mechanical terms, the latter is due to the overlap of the electron clouds of the two atoms, as the negatively charged electrons repel each other. At intermediate distances, however, there is a slight attraction between two such electron clouds from induced dipole–dipole interactions, physically due to electron correlation. Even if the molecule (or part of a molecule) has no permanent dipole moment, the motion of the electrons will create a slightly uneven distribution at a given time. This dipole moment will induce a charge polarization in the neighbour molecule (or another part of the same molecule), creating an attraction, and it can be derived theoretically that this attraction varies as the inverse sixth power of the distance between the two fragments.

The correct general shape, is the Morse potential, eq. (2.5). It does not have the $R-6$ dependence at long range, but as mentioned above, in reality there are also $R-8$, $R-10$, etc., terms.

$$U(r_{AB}) = D_{AB}[1 - e^{-\alpha_{AB}(r_{AB}-r_{AB,eq})}]^2$$

where D_{AB} is the dissociation energy of the bond and α_{AB} is a fitting constant. The hypothetical potential energy curve shown in Figure 2.1 can be reproduced over a much wider range of r by a Morse potential than by a quartic potential. Most force fields decline to use the Morse potential because it is computationally much less efficient to evaluate the exponential function than to evaluate a polynomial function (vide infra). Moreover, most force fields are designed to study the energetics of molecules whose various degrees of freedom are all reasonably close to their equilibrium values, say within 10 kcal/mol. Over such a range, the deviation between the Morse function and a quartic function is usually negligible.
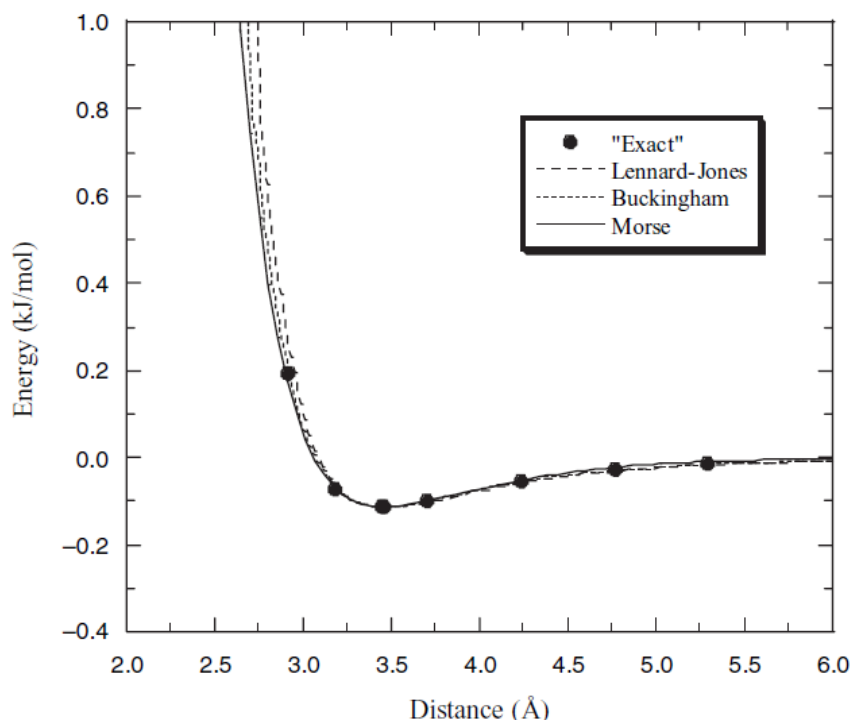
The van der Waals distance, R_0 AB, and softness parameters, ϵ_{AB}, depend on both atom types A and B. These parameters are in all force fields written in terms of parameters for the individual atom types. There are several ways of combining atomic parameters to di-atomic parameters, some of them being quite complicated. A commonly used method is to take the van der Waals minimum distance as the sum of two van der Waals radii, and the interaction parameter as the geometrical mean of the atomic "softness" constants.

$$R_0^{AB} = R_0^A + R_0^B$$
$$\varepsilon^{AB} = \sqrt{\varepsilon^A \varepsilon^B}$$

The electrostatic energy: charges and dipoles

This is due to internal (re)distribution of the electrons, creating positive and negative parts of the molecule. A carbonyl group, for example, has a negatively charged oxygen and a positively charged carbon. At the lowest approximation, this can be modelled by assigning (partial) charges to each atom.

The modelling of the electrostatic energy by (fixed) atomic charges has four main deficiencies:

(1) The fitting of atomic charges to electrostatic potentials focuses on reproducing *inter*molecular interactions, but the electrostatic energy also plays a strong role in the *intra*molecular energy, which determines conformational energies. For polar molecules the (relative) conformational energies are therefore often of significantly lower accuracy than for non-polar systems.

(2) The partial charge model gives a rather crude representation of the electrostatic potential surrounding a molecule, with errors often being in the 10–20 kJ/mol range. For a given (fixed) geometry, the molecular electrostatic potential can be improved

either by adding non-nuclear-centred partial charges, or by including higher order (dipole, quadrupole, etc.) electric moments.

(3) The coupling of electric charges and higher order moments with the geometry is neglected. Analysis has shown that both partial charges and higher order electric moments depend significantly on the geometry, i.e. these quantities do not fulfil the requirement of "transferability".

(4) Only two-body interactions are included, but for polar species the three-body contribution is quite significant, perhaps 10–20% of the two-body term.18 A rigorous modelling of these effects requires inclusion of atomic polarizabilities, but can be partly included in the two-body interaction by empirically increasing the interaction by 10–20%.

The bending energy

E_{bend} is the energy required for bending an angle formed by three atoms A—B—C, where there is a bond between A and B, and between B and C. Similar to E_{str}, E_{bend} is usually expanded as a Taylor series around a "natural" bond angle and terminated at second order, giving the harmonic approximation.

While the simple harmonic expansion is adequate for most applications, there may be cases where higher accuracy is required. The next improvement is to include a third order term, analogous to E_{str}. This can give a very good description over a large range of angles, as illustrated in the Figure below for CH_4. The "exact" form is again taken from electronic structure calculations (MP2/aug-cc-pVTZ). The simple harmonic approximation (P2) is seen to be accurate to about $\pm 30°$ from the equilibrium geometry and the cubic approximation (P3) up to $\pm 70°$.
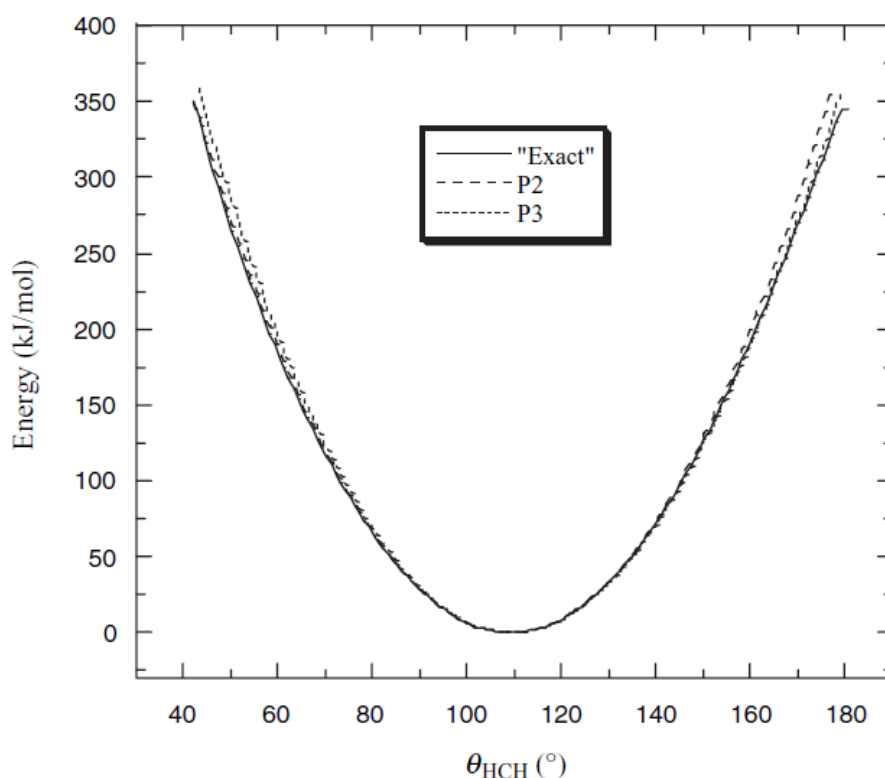
The out-of-plane bending energy
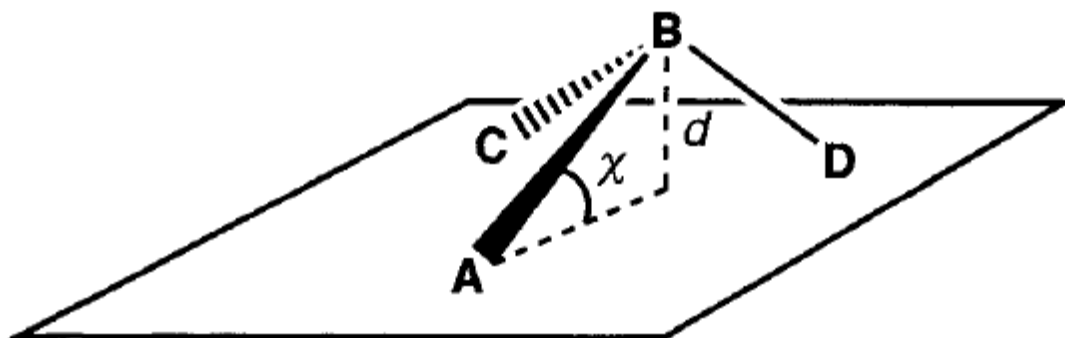
A special *out-of-plane energy bend* term (E_{oop}) is usually added, while the in-plane angles (ABC, ABD and CBD) are treated as in the general case above. E_{oop} may be written as a harmonic term in the angle χ (the equilibrium angle for a planar structure is zero) or as a quadratic function in the distance d, as given in equation below and shown in the above Figure.

$$E_{oop}(\chi) = k^B \chi^2 \quad \text{or} \quad E_{oop}(d) = k^B d^2$$

Such energy terms may also be used for increasing the inversion barrier in sp3-hybridized atoms (i.e. an extra energy penalty for being planar), and E_{oop} is also sometimes called E_{inv}.

The torsional energy

E_{tors} describes part of the energy change associated with rotation around a B—C bond in a four-atom sequence A—B—C—D, where A—B, B—C and C—D are bonded.
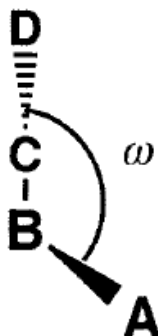
Looking down the B—C bond, the torsional angle is defined as the angle formed by the A—B and C—D bonds as shown in the above Figure. The angle ω may be taken to be in the range [0°,360°] or [−180°,180°]. The torsional energy is fundamentally different from E_{str} and E_{bend} in three aspects:

(1) A rotational barrier has contributions from both the non-bonded (van der Waals and electrostatic) terms, as well as the torsional energy, and the torsional parameters are therefore intimately coupled to the non-bonded parameters.

(2) The torsional energy function must be periodic in the angle ω: if the bond is rotated 360° the energy should return to the same value.

(3) The cost in energy for distorting a molecule by rotation around a bond is often low, i.e. large deviations from the minimum energy structure may occur, and a Taylor expansion in ω is therefore not a good idea.

To encompass the periodicity, E_{tors} is written as a Fourier series.

$$E_{tors}(\omega) = \sum_{n=1} V_n \cos(n\omega)$$

The $n = 1$ term describes a rotation that is periodic by 360°, the $n = 2$ term is periodic by 180°, the $n = 3$ term is periodic by 120°, and so on. The Vn constants determine the size of the barrier for rotation around the B—C bond. Depending on the situation, some of these Vn constants may be zero. In ethane, for example, the most stable conformation is one where the hydrogens are staggered relative to each other, while the eclipsed conformation represents an energy maximum.

Some authors divide these into *proper* dihedrals, where we might expect full rotation about the connecting bond B–C, and *improper* dihedrals where the rotation is limited. For example, if C–D were a C–H fragment of a methyl group we would be expect full rotation about B–C and a three-fold symmetry in the potential energy term. A–CH–CH– linkage in a benzene ring would only show a moderate flexing from its planar value (angle zero).

Cross terms

The first five terms in the general energy expression, eq. (2.1), are common to all force fields. The last term, E_{cross}, covers coupling between these fundamental, or diagonal, terms. Consider for example a molecule such as H_2O. It has an equilibrium angle of 104.5° and an O—H distance of 0.958Å. If the angle is compressed to say 90°, and the optimal bond length is determined by electronic structure calculations, the equilibrium distance becomes 0.968Å, i.e. slightly longer. Similarly, if the angle is widened, the lowest energy bond length becomes shorter than 0.958Å. This may qualitatively be understood by noting that the hydrogens come closer together if the angle is reduced. This leads to an increased repulsion between the hydrogens, which can be partly alleviated by making the bonds longer. If only the first five terms in the force field energy are included, this coupling between bond distance and angle cannot be modelled. It may be taken into account by including a term that depends on both bond length and angle. E_{cross} may in general include a whole series of terms that couple two (or more) of the bonded terms.

The components in E_{cross} are usually written as products of first-order Taylor expansions in the individual coordinates. The most important of these is the stretch/bend term, which for an A—B—C sequence may be written as in

$$E_{str/bend} = k^{ABC}(\theta^{ABC} - \theta_0^{ABC})[(R^{AB} - R_0^{AB}) - (R^{BC} - R_0^{BC})]$$

It has been suggested that the presence of cross terms (together with some other features) can provide a general way to classify force fields [Hwang *et al.* 1994]. A class I force field was considered one which is restricted to harmonic terms (e.g. for bond stretching and angle bending) and which does not have any cross terms. A class II force field would have anharmonic terms (e.g. through the use of Morse potentials or quartic terms) and explicit cross terms to account for the coupling between coordinates. The presence of these higher and cross terms would tend to improve the ability of the force field to predict the properties of more unusual systems (such as those which are highly strained) and also to enhance its ability to reproduce vibrational spectra. Another characteristic of a class II force field was that it could be used without modification to model the properties of isolated small molecules, condensed phases and macromolecular systems. It was subsequently suggested by Allinger [Allinger *et al.* 1996b] that a class III force field would also take account of chemical effects and other features such as electronegativity and hyperconjugation.

Force fields are determined by one of two routes. First of all, in an ideal world, one might calibrate their parameters against accurate quantum mechanical calculations on clusters of small molecules. The alternative is to calibrate against experimental data such as crystal structure, infrared absorption, X-ray measurements and liquid properties such as density, enthalpy of vaporization, Gibbs energies of solvation and the like.
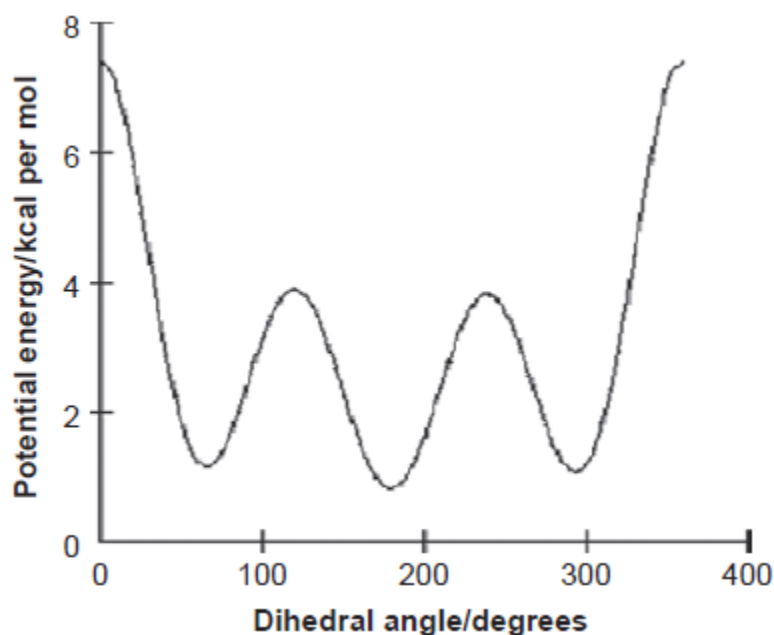
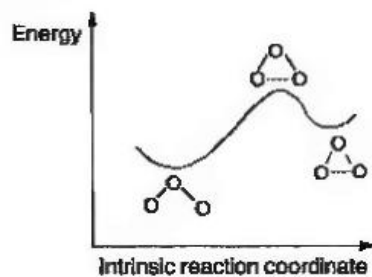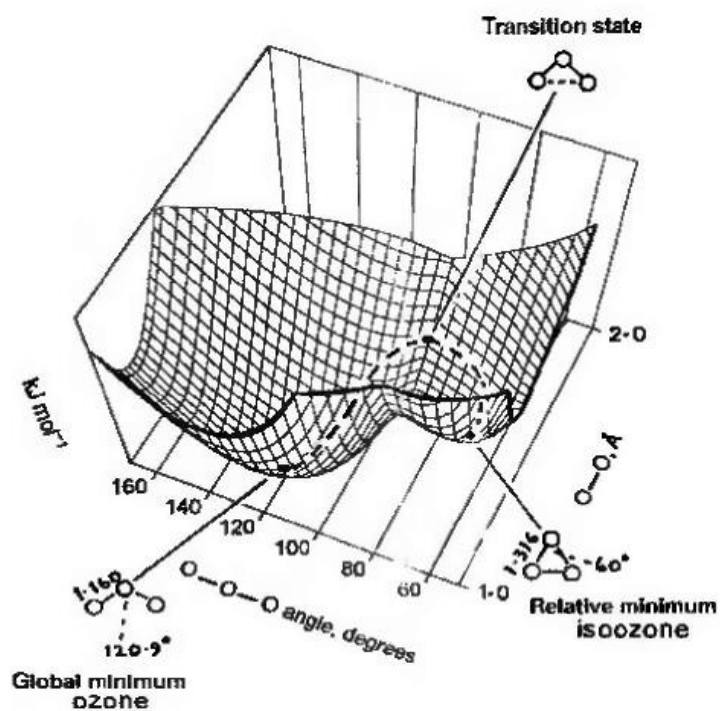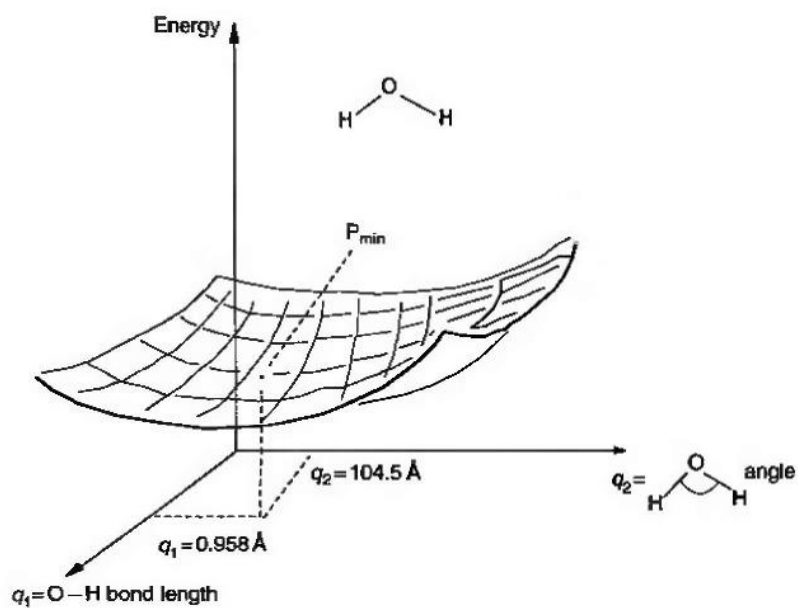**Assignment:**
Read the following research papers
1. Mayo *et al.* 1990, Dreiding force field
2. Rappé *et al.* (1992), 'a Full Periodic Table Force Field for Molecular Mechanics and Molecular Dynamics Simulations'

Potential Energy Surfaces

Consider now the substituted ethane CH2Cl–CH2Cl. A plot of the potential energy versus the ClC–CCl dihedral angle is shown in Figure 5.2. There are three minima, one lower than the other two. The three minima are referred to as *local minima* and the minimum at 180∘ is called the *global minimum*.


Plot of potential energy versus dihedral angle for CH₂Cl–CH₂Cl

Energy

$q_2 = 104.5$ Å

$q_1 = 0.958$ Å

$q_1 = $ O—H bond length

$q_2 = $ angle

P_{min}

Transition state

kJ mol⁻¹

O—O—O angle, degrees

O—O, Å

Relative minimum isoozone

Global minimum ozone

Energy

Intrinsic reaction coordinate

Mathematically, a stationary point is one at which the first derivative of the potential energy with respect to each geometric parameter is zero:

$$\frac{\partial E}{\partial q_1} = \frac{\partial E}{\partial q_2} = \cdots = 0 \qquad (2.1)$$

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The lowest energy pathway linking the two minima, the reaction coordinate or intrinsic reaction coordinate, is the path that is followed by a molecule which has acquired just enough energy to overcome the activation barrier, pass through the transition state, and reach the other minimum.
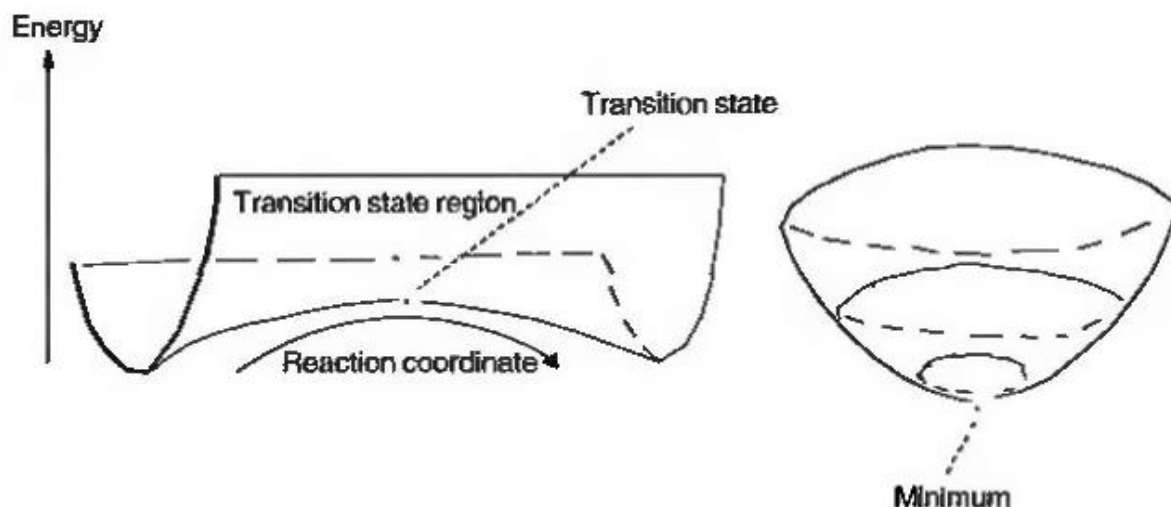
A transition state or saddle point and a minimum. At both transition state and the minimum $\partial E/\partial q = 0$ for all geometric coordinates q (along all directions). At the transition state $\partial E^2/\partial q^2 < 0$ for $q =$ the reaction coordinate and > 0 for all other q (along all other directions). At a minimum $\partial E^2/\partial q^2 > 0$ for all q (along all directions).

For a minimum

$$\frac{\partial^2 E}{\partial q^2} > 0$$

for all q.

For a transition state

$$\frac{\partial^2 E}{\partial q^2} > 0$$

for all q, *except along the reaction coordinate,* and

$$\frac{\partial^2 E}{\partial q^2} < 0$$

along the reaction coordinate.

The reaction coordinate is a composite of bond lengths, angles and dihedrals. A saddle point is a point on a PES, where the second derivative of energy with respect to only one (composite) coordinate is negative, is the transition state.

If, on a PES, there are other maximums where the second derivative with respect to other coordinates are negative, then these are known as higher order saddle points or hilltops.

## The Born-Oppenheimer Approximation

A PES is a plot of energy (of nuclei and electrons) against the geometric coordinates of the nuclei. Electron coordinates are not plotted because they are lighter than nuclei and hence, a good approximation is that the nuclei remain stationary with respect to electrons. Actually, the nuclei vibrate about an equilibrium position with a small amplitude and this is assumed to be stationary. As a consequence, the molecule has a shape. Each point in the PES corresponds to a set of stationary nuclei.

Geometry Optimization

The process of locating a stationary point on a PES by calculating it geometry and energy is called geometry optimization. All three types of stationary points (a minimum, a transition state and higher order saddle points) are considered.

Process:

Input a structure that is near to the desired stationary point to a quantum chemical software. The program systematically changes the geometry until it has found a stationary point. The curvature at this point (second derivative is negative or positive) is used to decide whether it is a saddle point or a minimum.
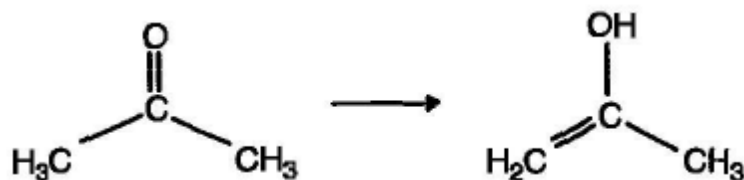
The spectrum of the mixture suggested the presence of enol isomer of propanone. Computation of the IR can resolve the problem. But which conformer? Rotation about C-O and C-C bonds creates six possible stationary points.
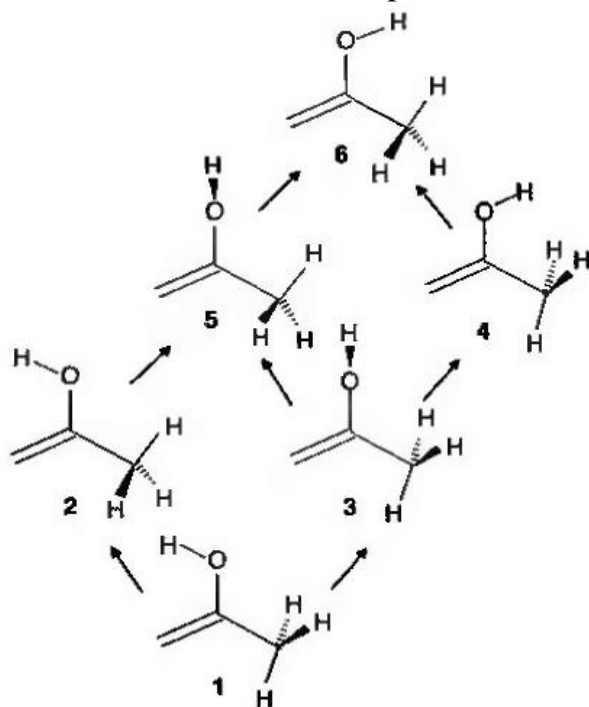

One (1) is global minimum and 4 is a relative minimum, while 2 and 3 are transition states and 5 and 6 are hilltops. AM1 calculations gave relative energies for **1, 2, 3** and **4** of 0, 0.6, 14 and 6.5 kJ mol^{-1}, respectively (**5** and **6** were not optimized). The arrows represent one-step (rotation about one bond) conversion of one species into another.

Algorithm: Consider a 1D PES. Let the input structure be $P_i(E_i, q_i)$ and the nearby minimum be $P_0(E_0, q_0)$. Assume that near the minimum the potential energy is a quadratic function of q. Then

$$E - E_0 = k(q - q_0)^2$$

At the input point

$$(dE/dq)_i = 2k(q_i - q_0)$$
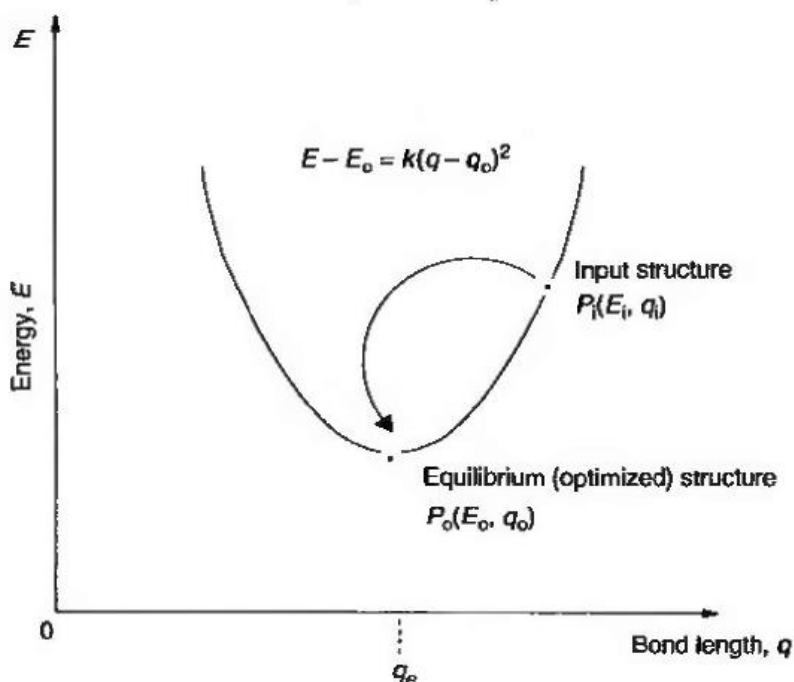
At all points

$$d^2E/dq^2 = 2k \; (= \text{force constant})$$

$$(dE/dq)_i = (d^2E/dq^2)(q_i - q_0)$$

and

$$q_0 = q_i - (dE/dq)_i/(d^2E/dq^2)$$

Therefore, if we know the slope or gradient of the PES$(dE/dq)_i$, the curvature at the point of initial structure$(d^2E/dq^2)_i$, and the initial geometry then we can calculate the optimized geometry q_0.

$$\mathbf{g_i} = \begin{bmatrix} (\partial E/\partial q_1)_i \\ (\partial E/\partial q_2)_i \\ \vdots \\ (\partial E/\partial q_9)_i \end{bmatrix} \qquad \mathbf{H} = \begin{bmatrix} \partial^2 E/\partial q_1 q_1 & \partial^2 E/\partial q_1 q_2 & \cdots & \partial^2 E/\partial q_1 q_9 \\ \partial^2 E/\partial q_2 q_1 & \partial^2 E/\partial q_2 q_2 & \cdots & \partial^2 E/\partial q_2 q_9 \\ \vdots & \vdots & \cdots & \vdots \\ \partial^2 E/\partial q_9 q_1 & \partial^2 E/\partial q_9 q_2 & \cdots & \partial^2 E/\partial q_9 q_9 \end{bmatrix}$$

The force constant or the second derivative matrix is called the Hessian. In the Hessian $\partial^2 E/\partial q_1 q_2 = \partial^2 E/\partial q_2 q_1$